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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
01121-T8341.NP.CON

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on December 8, 2008

Signature Judy Anderson

Typed or printed name Judy Anderson

Application Number	Filed
10/723,435	11/26/2003

First Named Inventor: Weihong Xiong, et al.

Art Unit	Examiner
1611	Ghali, Isis

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☑ attorney or agent of record.
Registration number 44,989.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Signature

David W. Osborne
Typed or printed name

801 566 6633
Telephone number

12/8/2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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REASONS FOR PRE-APPEAL BRIEF REVIEW

In the Final Office Action dated September 22, 2008; the Examiner maintained the following rejections: Claims 81-84, 86, 102, and 103 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over U.S. Patent No. 6,352,715 (hereinafter U.S. '715) in view of U.S. Patent No. 6,365,178 (hereinafter U.S. '178). Claims 53-84, 86-97, are 102-103 pending while claims 53-80, and 87-97 have been withdrawn.

In the following discussion, Applicants have focused on specific arguments that were made in the response to the previous non-final Office Action that were overlooked and specific aspects of the claimed invention which are clearly not taught or suggested by the cited reference. This does not preclude Applicants from arguing additional deficiencies in the cited references during any later Appeal proceedings or prosecution.

Rejections Under 35 U.S.C. § 103

Before discussing the obviousness rejections herein, it is thought proper to briefly state what is required to sustain such a rejection. The issue under § 103 is whether the PTO has stated a case of *prima facie* obviousness. A *prima facie* case of obviousness requires: (1) some reasoning or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teaching; (2) a reasonable expectation of success; and (3) the art reference or combination of references must teach all of the claim limitations (MPEP 2142). The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the art, not in the applicants' disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ 2d. 1438 (Fed. Cir. 1991) (MPEP 2143). Nothing in the recent *KSR* Supreme Court case changes this basic analysis.

The Examiner has asserted that a *prima facie* case of obviousness is found in the combination of U.S. Patent No. 6,352,715 (hereinafter U.S.'715) with U.S. Patent No. 6,365,178 (hereinafter U.S. '178) renders the presently pending claims unpatentable. As outlined in the previous office action, U.S. '715 is drawn to a transdermal delivery system for Huperzine A. *See* Abstract. Generally, the '715 reference focuses on pH as a means to increase permeation of the drug and concludes that the only form of huperzine able to penetrate the skin is the neutral form. *See* col. 2, lines 65-67. The '715 reference speculates that a possible method to further improve

delivery of the neutral form of huperzine is to increase concentration of undissociated huperzine at the huperzine source by adding non-polar solvents such as alcohols and glycols. *See* col. 8, lines 41-49. The Examiner has relied on U.S. '178 to allegedly show the teachings of an adhesive matrix patch and the specific permeation enhancers of the present claims. The Examiner has not provided any teaching, suggestion, or motivation found in the cited references themselves to form the cited combination nor has the Examiner provided any finding that there was reasonable expectation of success. Rather the Examiner has relied on the assertion that the necessary teaching, suggestion, or motivation to combine the references teachings was in the knowledge generally available to one of ordinary skill in the art. Applicants vigorously dispute the Examiner's assertion of the knowledge of the ordinary skill in the art.

As discussed in previous office action responses, transdermal drug delivery is a very complex and delicate art. For example, permeation or penetration enhancers for specific active agents are not easy to identify. The Applicants submit that such teachings regarding the fickle and unpredictable nature of penetration enhancers are generally known in the art. There are numerous examples of third party teachings regarding the difficulty of formulating transdermal matrix patches, and in particular selecting and formulating with permeation enhancers. For example, U.S. Patent No. 5,500,222 which also describes permeation enhancers in the same fashion:

> No "universal" permeation enhancer has been identified. Instead, the behavior of permeation enhancers is highly idiosyncratic; a permeation enhancer effective for one drug may not be effective with other drugs, including closely related drugs.
>
> Often, a permeation enhancer will exacerbate irritation and sensitization problems by allowing high transdermal permeation rates of the drug or permeation enhancer or permitting otherwise impermeable components of the transdermal device to enter the skin. Many potential permeation enhancers interact adversely with other components of transdermal devices. One major problem is that many potential permeation enhancers are not compatible with medically acceptable contact adhesives. Enhancers may improve the transdermal permeation rate adequately, but not adequately reduce the lag time.
>
> The use of a permeation enhancer in any transdermal drug delivery device necessarily complicates the design and development of the device. Permeation enhancers cause compatibility problems throughout the delivery system. Instead of having to characterize the properties of the reservoir compositions, adhesives, and release-controlling materials with respect to just the drug, these materials must now have

> the proper characteristics with respect to both the drug and the permeation enhancer. Typically, drugs and permeation enhancers have very different physical and chemical properties, and, in most cases, the properties of mixtures of the drug with the permeation enhancer are unknown. For example, permeation enhancers can cause, among other problems, cohesive failure of adhesives and can partition through other components in the system. See col. 2, line 47 through col. 3, line 12.

Another similar third party statement regarding the complexity unpredictability of permeation enhancement in the transdermal arts is found in U.S. Patent No. 7,214,381 which states in part:

> To be accepted a permeation enhancer or combination thereof should have the ability to enhance the permeability of the skin for the drug, should be non-toxic, non-irritant and non-sensitizing on repeated exposure. It is often difficult to predict which compounds will work as permeation enhancers and which permeation enhancers will work for particular drugs. In transdermal drug delivery applications, a compound that enhances the permeability of one drug or a family of drugs may not necessarily enhance the permeability of another drug or family of drugs.... Therefore, the usefulness of a particular compound(s) or mixture thereof as a permeation enhancer must be carefully analyzed and demonstrated by empirical work.

Col. 2, lines 4-20.

Applicants submit that the above teachings regarding the difficulty of formulating transdermal systems and identifying permeation enhancers are ample evidence the knowledge of those of ordinary skill in the art. Specifically, Applicants assert that the above passages demonstrate that, based on the knowledge in the art, of one of ordinary skill in the art would not have had reason to combine the cited references nor would they have had reasonable expectations of success in forming such a combination. In fact, the teachings of U.S. '715 provide additional evidence as to the difficulty and unpredictability of formulating with permeation enhancers when it states: "[a] possible method to increase the concentration of undissociated form of Hup A may be to add non-polar solvents such as alcohols and glycols. However, these agents also reduce partitioning of drugs into the skin. Thus various co-solvents need to be evaluated to achieve balance of satisfactory solubility and partitioning." Col. 8, lines 47-52. In light of the above discussion, Applicants assert that the Examiner has not establish a *prima facie* case of obviousness because the Examiner has not shown proper teaching,

suggestion, or motivation found in either the references themselves or in the knowledge of one of ordinary skill in the art. Accordingly, Applicants submit that the rejection should be withdrawn.

Further, Applicants note that, although U.S. '178 sets forth a lengthy laundry list of possible permeation enhancers and/or cell envelope disordering compounds which can be used in the matrix patches, including the broad category of "saturated and unsaturated fatty acids and their esters," the only teaching of a fatty acid ester of lactic acid as a permeation enhancer is found in Example 11. Example 11 is drawn to specific transdermal formulations for diclofeanc, buspirone, and clonidine, each of which is not only distinct drug from Huperzine, but is also in a distinct family of drugs far removed from Huperzine. Nothing in U.S. '178 correlates or connects the use of lactic acid esters, or any other permeation enhancer, with Huperzine or any other Anti-Parkinson drug. As set forth above, the identification and correlation of specific permeation enhancers with specific drugs is "difficult to predict" and "must be carefully analyzed and demonstrated by empirical work." Accordingly, Applicants submit that the indiscriminate combination of the transdermal system of U.S. 715 with a permeation enhancer found in U.S. '178 without teaching, suggestion or motivation for such a combination found in the references themselves or in the knowledge of one of ordinary skill in the art, and without having a reasonable likelihood of success is evidence of impermissible hindsight reconstruction. As noted by the Examiner, reconstruction based upon hindsight reasoning is permissible only "so long as it takes into account only knowledge which was within the level of the ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from the applicant's disclosure..." *In re Mclaughlin,* 443 F.2d 1392. As set forth above, at the time of the present invention and based on the knowledge of one of ordinary skill in the art, there was no teaching, suggestion, motivation or reasonable likelihood of success which would have prompted one of ordinary skill to have combined the teachings of the asserted references. Accordingly, Applicants submit that the combination has is made using impermissible hindsight and is therefore improper.

Lastly, the Examiner has conceded that the presently claimed blood plasma levels of huperzine are not taught by U.S. '715, but continues to assert that such blood plasma levels can be readily determined by one having ordinary skill in the art and are inherently taught by U.S.

'715. Applicants continue to dispute these assertions. Specifically, Applicants dispute that the claimed blood plasma levels could be readily achieved through simple experimentation or "tinkering" with other transdermal formulations. Blood plasma levels are the key of the formulation design of transdermal delivery system, which is affected by numerous factors including selection of proper adhesive, selection of proper enhancers and its load, drug load, delivery rate, and depletion rate. Further, the present claims require specific blood plasma levels for a period of at least three days. Accordingly, the Examiner's assertion that the teaching in U.S. '715 of overlapping delivery rates is insufficient to disclose the claimed blood plasma levels.

For all of the above described reasons, Applicants assert that the cited references fail to provide a *prima facie* case of obviousness and respectfully request that the rejection be withdrawn and the pending claims allowed.

CONCLUSION

In view of the foregoing, Applicant believes that the present rejections are unsustainable and should be withdrawn. Therefore, Applicant respectfully requests that the prosecution be reopened and/or the claims be allowed. If any impediment to the allowance of these claims remains after consideration of the above remarks, and such impediment could be resolved during a telephone interview, the Examiner is invited to telephone Mr. David Osborne, at (801) 566-6633 to address such issues as expeditiously as possible.

Dated this 8th day of December, 2008.

Respectfully submitted,

THORPE, NORTH & WESTERN, LLP

/davidwosborne/

David W. Osborne

Reg. No. 44,989
8180 South 700 East, Suite 350
Sandy, UT 84070
Telephone: (801) 566-6633
Facsimile: (801) 566-0750

DO/SS:ja